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(54) Title: PHARMACEUTICAL FORMULATION OF SODIUM AMOXYCILLIN AND POTASSIUM CLAVULANATE

(57) Abstract

Pharmaceutical formulations comprising crystalline sodium amoxycillin and potassium clavulanate (2000/200mg and 1000/100mg), adapted for iv administration and provided as unit dosages in a vial having a desiccant stopper.

PHARMACEUTICAL FORMULATION OF SODIUM AMOXYCILLINE AND POTASSIUM CLAVULANATE

This invention relates to a pharmaceutical formulation comprising a combination of the antibiotic amoxycillin and the beta-lactamase inhibitor potassium clavulanate adapted for administration by intravenous injection (iv), to vials containing such formulations, to the use of such formulations in therapy and to methods for the manufacture of such formulations.

The combination of the antibiotic amoxycillin, as amoxycillin trihydrate, and potassium clavulanate, is a well known and widely used medicament for bacterial infections, marketed by SmithKline Beecham in many countries under the trade mark Augmentin. Formulations already available for oral administration include various tablet types, paediatric suspensions, chewables and granules in sachets. These comprise amoxycillin and clavulanate in a variety of ratios, 2:1, 4:1, 7:1 and 8:1, depending on the particular formulation, for either a three times a day (tid) or, more recently, a twice a day (bid) dosage regimen.

In addition, there are also available formulations adapted for iv administration. Regulatory approval has been obtained by SmithKline Beecham in various European countries for a product consisting of sodium amoxycillin and potassium clavulanate in the weights 250/25mg, 500/100mg, 1000/200mg and 2000/200mg (amoxycillin/potassium clavulanate, expressed as the weight of the corresponding free acid). In such existing, approved formulations, the amoxycillin component is provided by spray-dried sodium amoxycillin. This has an inherent desiccating capacity which helps to protect the potassium clavulanate component from hydrolysis by moisture from a number of sources. Such formulations are marketed by SmithKline Beecham under the trade name Augmentin, for reconstitution as an intravenous injection or infusion, for treatment of *inter alia* upper respiratory tract , lower respiratory tract, genito-urinary tract, skin and soft tissue and bone and joint infections.

In addition to the above mentioned products, other versions of an injectable product containing either 500/100mg or 1000/200mg amoxycillin/potassium clavulanate are available in a limited number of countries, from the Slovenian company Lek. It is believed that crystalline sodium amoxycillin has been used in some batches but samples of such products have been found to discolour and deteriorate.

European patent application EP 0 131 147-A1 (Beecham Group plc) describes a further form of sodium amoxycillin, crystalline sodium amoxycillin. This is

anhydrous, non-hygroscopic, with a high degree of stability. Furthermore, it is essentially pure, in contrast to the lesser degree of purity achievable with the spray-dried form. Crystalline sodium amoxycillin is said to be suitable for incorporation into a formulation further comprising potassium clavulanate, adapted for parenteral administration. No details are however provided of specific formulations, either by weight of drug substance or ratio, or of a dosage regimen.

Whilst crystalline sodium amoxycillin is available in a purer state than spray-dried sodium amoxycillin, it lacks the inherent desiccating properties of the spray-dried version, which means that alternative means have to be devised to protect the formulation from moisture. This moisture arises from moisture in the atmosphere, which may penetrate through the packaging, for instance a vial stopper, during storage of a packed product. It is also present as moisture picked up by the sodium amoxycillin and potassium clavulanate during initial manufacturing, blending and packaging operations.

Various proposals have been suggested, to solve this problem, for instance incorporating some desiccating capacity into the packaging device, as described in WO 95/25045, WO 95/34488, and WO 96/04189 or by the addition of a desiccant material to the formulation, as described in WO 95/33487 (all to SmithKline Beecham). In particular, WO 96/04189 describes *inter alia* containers with closures formed from an elastomeric material compounded with a desiccant material such as calcium oxide or molecular sieve (so-called desiccant stoppers). Such containers are said to be particularly suitable for use with mixtures of potassium clavulanate and crystalline sodium amoxycillin.

In addition, DeGrazio and Flynn (J Parenteral Science and Technology, 46(2), 1992, 54-61) describe lyophilisation closures for protein based drugs. Such drugs are normally extremely sensitive to moisture and also present in only small quantities, typically about 10mg. The components of the closure are carefully selected to minimise the amount of residual water in the closure, after manufacture, so that there is less moisture which can then enter the vial and attack the contents thereof. It is also suggested that a small amount of molecular sieve (up to 10 parts per hundred rubber) may be added, as a "moisture trap" to retain any residual moisture in the stopper material and prevent it leaching into the vial.

There remains a continuing need for new and improved formulations comprising amoxycillin and potassium clavulanate and adapted for iv administration to be made available, to provide physicians with further means of treating bacterial infections, in

particular more serious infections in a hospital environment or patients otherwise unsuitable for oral therapy.

Accordingly, the present invention provides for a pharmaceutical formulation adapted for intravenous administration and consisting essentially of crystalline sodium amoxycillin and potassium clavulanate in the weight ratio 10:1.

When used herein, the weights of sodium amoxycillin and potassium clavulanate are expressed, for convenience, as the equivalent weights of the corresponding free acids, amoxycillin and clavulanic acid, respectively. It will also be appreciated that, in determining the actual quantity to be included in a formulation, due allowance will be made for the potency (activity) of the sodium amoxycillin and potassium clavulanate, according to procedures well known in the art.

Preferably, the crystalline sodium amoxycillin is anhydrous. Preferably the sodium amoxycillin is sterile.

A preferred formulation is provided as a unit dosage which comprises 2000mg crystalline sodium amoxycillin and 200mg potassium clavulanate, within a tolerance of ±10%. Preferably, the formulation has no added excipients or carriers.

A further preferred formulation is provided as a unit dosage which comprises 1000mg crystalline sodium amoxycillin and 100mg potassium clavulanate, within a tolerance of ±10%. Preferably, the formulation is provided as a unit dosage which consists essentially of 1000mg crystalline sodium amoxycillin and 100mg potassium clavulanate, within a tolerance of ±10%.

Preferably, a 2.2g formulation (consisting of 2000mg amoxycillin and 200mg clavulanate) is used in a twice a day (bid, q12hr) or a three times a day (tid, q8hr) dosage regimen and a 1.1g formulation (consisting of 1000mg amoxycillin and 100mg clavulanate) is used in a twice a day (bid, q12hr) or a three times a day (tid, q8hr) dosage regimen. Such formulations may also be more frequently, at the discretion of the physician.

Preferably, the bid administration is at 12 hour intervals, although a greater or lesser interval between administrations may be used. Preferably, the tid administration is at 8 hour intervals, although a greater or lesser interval between administrations may be used.

For use, the formulation will be reconstituted as an aqueous solution and may be administered either by slow intravenous injection over a period of 3-4 minutes directly into a vein or via a drip tube or, preferably, by infusion, preferably over a period of 60 min. Preferably, the 2.2g formulation is administered only by infusion. For an intravenous injection, the preferred diluent is Water for Injections BP. For the 1.1g formulation, preferably 20ml diluent is used. For intravenous infusion, the 1.1 and 2.2g formulations are preferably reconstituted by the addition of infusion fluid (an initial volume of 20ml which is then immediately diluted to 100ml). Preferred infusion fluids include Sodium Chloride intravenous infusion BP (0.9%w/v), Water for Injections BP, Sodium Lactate Infusion BP (M/6), Compound Sodium Chloride Injection BPC 1959 (Ringer's), and Compound Sodium Lactate Intravenous Infusion BP (Ringer-Lactate:Hartmann's), of which Sodium Chloride intravenous infusion BP (0.9%w/v) is more preferred. It will be appreciated that reconstituted formulations have limited stability (up to 90min for the 2.2g formulation and up to 120min for 1.1g formulation) and accordingly should be administered without undue delay, for instance no more than 30 and 60 minutes after reconstitution for the 2.2g and 1.1g formulations, respectively, allowing for a 60min period for infusion.

Further formulations include unit dosages which comprises 250mg crystalline sodium amoxycillin and 25mg potassium clavulanate, or 500mg crystalline sodium amoxycillin and 50mg potassium clavulanate, within a tolerance of ±10%. Preferably, the formulation has no added excipients or carriers.

In order to provide a unit dosage formulation of the present invention in a vial which has a useful shelf life, for instance at least one year, preferably two or more years, it is preferred to use a the vial provided with desiccating means, to remove water which is picked up on the surface of the crystals of potassium clavulanate during the packaging process, from the interior of the vial, at a rate sufficient to reduce degradation of the clavulanate to an acceptable level. Such desiccating capacity may be provided by using a so-called "desiccant" stopper. Preferred desiccant stoppers are described in WO 96/04189 (SmithKline Beecham) and WO 97/29151 (The West Company (UK) Ltd).

Accordingly, in further aspect, the present invention provides a vial having a desiccant stopper made at least in part from a desiccant elastomeric material and containing crystalline sodium amoxycillin and potassium clavulanate, as hereinbefore defined.

In a preferred aspect, the vial contains essentially 2000mg crystalline sodium amoxycillin and 200mg potassium clavulanate or 1000mg sodium amoxycillin and

100mg potassium clavulanate, within a tolerance of ±10%, preferably with no added excipients or carriers.

As used herein, the term "desiccant elastomeric material" refers to an elastomeric material which comprises essentially an elastomeric base material compounded with a desiccant material, and optionally further comprising additional ingredients selected from a filler, an acid acceptor, a curative pigment and a processing aid.

The compounding of the elastomeric base material with a desiccant material causes the resultant desiccant elastomeric material to exercise a desiccant effect upon the interior of the container. The quantity of elastomeric base material compounded with a desiccant material should be sufficient to ensure absorption of sufficient of the water vapour in the container, or water in or on the material contents of the vial and its surfaces, to prevent or reduce to an acceptable degree any degradation of the material by the said water or water vapour.

The elastomeric material may further comprise additional reinforcing fillers, preservatives, antioxidants, additives etc. to modify its stiffness, chemical resistance and other properties.

The elastomeric base material may be a rubber. Such a rubber may be a natural rubber, or a synthetic rubber such as a butadiene-based rubber, e.g. based on styrene-butadiene or *cis*-1,4-polybutadiene, butyl rubber, halogenated butyl rubber, ethylene-propylene rubber, neoprene, nitrile rubber, polyisoprene, silicone rubber, chlorosulphonated polyethylene or epichlorhydrin elastomer, or a mixture, blend or copolymer thereof. Halobutyl, e.g. bromobutyl, chlorobutyl, rubbers and silicone rubbers are pharmaceutically acceptable rubbers known for use as materials for stoppers etc. to be maintained in contact with pharmaceutical products. Such elastomeric materials are sufficiently permeable to atmospheric water vapour that the desiccant material compounded with the rubber can exert its desiccant effect through a thin layer of the material. Preferably, the elastomeric base material is a halogenated butyl rubber, more preferably a chlorinated or a brominated butyl rubber, which may be a copolymer and/or blend with other suitable co-polymers, particularly other elastomers and rubbers. Preferred copolymers/blend for use in making stoppers for pharmaceutical vials are well known.

The ingredients e.g. filler, desiccant etc. and others identified below are normally used as powders and are preferably in a particle size of less than 20 micron, more preferably 10 micron or less, for instance from 1 to 10 micron.

Preferably, filler is present in the range 0 to 100phr, more preferably 0 to 50phr, yet more preferably, 20 to 50phr, most preferably 35 to 45 phr, particularly around 40±2phr. Preferred fillers include talc and clay, for instance a calcined clay, or a mixture of such filler materials, for instance a mixture of a talc and a clay. The filler and the elastomeric base material should be mutually inert to each other. Representative examples of talcs and clays for use as fillers in stoppers for pharmaceutical vials are well known and include talcs such as Luzenac Mistrobond. Other talc-like materials which may also be used include finely powdered alumino silicates and other metal silicates. Conventional reinforcing fillers include inorganic reinforcing fillers such as china clay and other clays.

The term "phr" refers to "parts per hundred rubber". It is term commonly used in the rubber and elastomer industry, and in which "rubber" refers to the elastomeric materials comprising the base for the material.

The desiccant material should be one which is inert relative to the elastomeric material, and *vice versa*. Furthermore, the desiccant material should be one which can chemically or physicochemically absorb or fix absorbed water, e.g. by formation of a hydration product, so that there is a reduced possibility of subsequent reversible release of the absorbed water, which might for example occur if the temperature of the desiccant material should rise, e.g. to around 40°C subsequent after earlier desiccation at a lower temperature.

Preferably, the desiccant material is an inorganic desiccant material which is wholly or substantially insoluble in water so that none or only a pharmaceutically insignificant amount of the desiccant material or its hydration product, or undesirable ions, is likely to enter solution during the period when the stopper is in contact with water or aqueous medium, following reconstitution. Particularly preferred desiccant materials include dried molecular sieve, especially a sieve of the zeolite type, calcium oxide, desiccating magnesium oxide or mixtures thereof. Calcium oxide chemically fixes water by formation of calcium hydroxide, from which water can only be released at extreme temperatures. Absorbed water can generally only be released from molecular sieves at several hundred °C, that is, well above the temperatures containers of pharmaceutical substances would be expected to experience under normal storage. Representative examples include the products sold in the UK under the names Molecular Sieve 4A, Grace A3™, Siliporite™ and Ferben 200™.

Preferably, inorganic desiccant is present in the range 20 to 100phr, more preferably 30 to 80phr, most preferably 30 to 50phr. The appropriate quantity for a particular application may be readily determined experimentally.

Preferably, a desiccant stopper for use in the present invention is compounded from a halobutyl, e.g. chlorobutyl, rubber and an inorganic desiccant such as a molecular sieve or calcium oxide, more preferably, a chlorobutyl rubber compounded with a molecular sieve.

Acid acceptors may be usefully incorporated, to bind halogens such as bromine that may be liberated from the rubber. Preferred acid acceptors include magnesium oxide and zinc oxide, incorporated in the range 0.5 to 10phr, preferably from 3 to 7phr. Magnesium oxide is preferably present in the range 5 to 7phr. .Zinc oxide is preferably present in the range 3 to 6phr.

Curative agents may be usefully included to form cross links in the rubber. Preferred such agents include elemental sulphur, incorporated in conventional amounts. Other curative agents include halogenated phenolic resin, peroxides and alkylated resins.

Pigments which may be incorporated include titanium oxide and carbon black. Typically a blend of titanium dioxide and carbon black is used, to give a dark grey product.

Processing aids may be incorporated to prevent sticking of the elastomeric material in the blending process and to moulds, etc. Examples of such aids conventionally used for stoppers for pharmaceutical vials include stearic acid and /or other fatty acids, such as blends of fatty acids, waxes such as polyethylene, silicones etc..

Preferably, the desiccant elastomeric material comprises:
100 phr of an elastomeric base material;
from 0 to 110 phr of a filler; and
from 20 to 100 phr of an inorganic desiccant.

More preferably, the desiccant elastomeric material comprises as its essential ingredients (within ±10% tolerance):

Halogenated butyl rubber	100phr;
Talc, clay or talc/clay mixture (filler)	40;
Molecular sieve desiccant	40; and

curative, acid acceptor, processing aids and pigment, present in from 0.5 to 15phr (combined total).

Such rubbers may be compounded in the manner with which they are conventionally compounded for manufacture of a stopper as known in the art of manufacture of rubber stoppers.

The compounding process typically comprises the following process steps:
(1) Activation of the inorganic desiccant, typically for a molecular sieve at 350° for 16h in an oven. This may be followed by lay out and storage if necessary under dry conditions. For most molecular sieves suitable activation and subsequent storage conditions are defined by the supplier. Some desiccants may be obtained from their supplier already activated, or may not need activation, so activation is an optional step.
(2) Weighing of the ingredients.
(3) Mixing of the ingredients in a suitable mixer. This mixing step generally produces a roughly homogenized mixture of the ingredients.
(4) Stock blending, for example milling and blending. This step mixes the ingredients more completely and also generates heat and pressure.
(5) Calendering, i.e. extrusion and shaping. The shaped rubber may if necessary be stored for subsequent moulding under suitably dry conditions.
(6) Moulding, e.g. injection moulding or compression moulding to form a shaped end product such as a stopper as described above.
(7) Trimming of the shaped elastomer and dipping in a trim solution.
(8) Washing and drying of the end product.
These processing steps are generally conventional in the art of elastomer product manufacture such as rubbers. After manufacture solid products such as stoppers made of the elastomeric material of this invention are preferably stored in a container sealed against ingress of atmospheric moisture.

A stopper for use in the present invention is may be made wholly of the said desiccant elastomeric material. Stoppers may also be made only partly of the said desiccant elastomeric material.

Preferably parts of the stopper which engage the mouth opening are at least partly, more preferably wholly made of an elastomeric material comprising a natural or synthetic rubber (which may be the above-described desiccant elastomeric material), thereby allowing a tight compression fit with the mouth of the vessel. The sealing engagement of the closure with the mouth opening may be by a generally conventional

construction e.g. similar to a conventional stopper. For example the stopper may be engaged with the rim of the neck of a vial by a screw thread, a friction/compression fitting, and/or a circlip-type clamp around the neck of the vial. Such constructions are known in the art. The stopper may seal the mouth in a generally conventional manner, e.g. by a compression fitting of the closure wall against the rim of the mouth, or by a sealing ring compressed between the closure face and the rim of the mouth etc.

Preferably, the stopper comprises a puncturable region in direct communication with the interior of the vial, through which a hypodermic needle may be inserted The puncturable region may suitably comprise a thinned region, and is preferably provided in a region of elastomeric material (which may comprise the desiccant material) which can resiliently seal around a hypodermic needle which is inserted therethrough, so as to facilitate sterile insertion and withdrawal. Water may be introduced into the vessel by means of a hypodermic needle puncturing the closure face through the puncturable region, so as to dissolve the contents, and the so-formed solution then withdrawn via the needle, for administration.

Conveniently, the closure, including the puncturable region, may all be made of the desiccant elastomeric material. Such a vial closure may correspond in shape and size to conventional vial closures made of elastomeric material, and may be retained on the mouth of the vial by a conventional metal circlip. Such conventional vial closures also include closures for use in the ADD-vantage (Trade mark) system, from Abbott. Desiccant elastomeric materials may be moulded into such shapes and sizes by a moulding process entirely analogous to that used to mould closures out of conventional elastomeric materials such as rubbers.

Alternatively, the closure may be of multi-part construction having only parts, including those parts which are exposed to the interior of the vial body, made of the said desiccant elastomeric material. Other parts of the stopper which are not made of desiccant elastomeric material and which come into contact with the atmosphere within the vial may be made of generally conventional materials, preferably pharmaceutically acceptable materials, such as plastics materials, elastomeric materials etc., or composite materials such as metal and plastics or elastomeric materials. Preferably such parts are made of plastics or elastomeric materials which are of low moisture content, of low moisture permeability and low moisture affinity.

The distribution of the desiccant elastomeric material may be such that the desiccant elastomeric material is located on only part of the closure wall of the stopper, so that for example the puncturable region may be situated between areas of the closure wall

on which is the desiccant polymer, or to one side of such an area, thereby facilitating the construction of the puncturable region as a thinned region of the closure face.

Such a multi-part construction includes the possibility that the closure may be integrally made of a co-moulded, or fused together, desiccant elastomeric material and an elastomeric or plastics material making up parts of the structure of the stopper. Alternatively, the desiccant elastomeric material may be provided as a separate part, retained by the closure on a suitable inward surface, e.g. in an inwardly facing holder or cavity.

Preferred embodiments of stoppers having multi-part construction are described in WO 96/04189 (SmithKline Beecham).

Preferred stoppers for use with formulations of the present invention are able to take up atmospheric moisture at 30% RH or less, preferably at 10%RH or less. Preferred stoppers exercise such a desiccant function for a long period, ideally throughout the shelf life of the formulation, typically two years.

Preferred stoppers should also be capable of being washed and sterilised, without loss of their desiccant ability at these low RH values. For example, desiccant polymer vial closures are ideally sterilised by gamma irradiation prior to use, without loss of their desiccant ability. It is found that desiccant rubbers such as halogenatedbutyl, e.g. chlorobutyl, rubber compounded with calcium oxide or molecular sieves are capable of being washed without a significant deleterious effect on their desiccant ability. Alternatively, stoppers may be re-activated by microwave radiation as described in WO 98/17711 (SmithKline Beecham).

The nature and quantity of desiccant material to be used in a stopper can be readily determined by straightforward experimentation or calculation, e.g. from the moisture content of the contents of the vial. Suitably for use with formulations according to the present invention, the stopper should scavenge up to 25 milligrams of water with a residual RH of less than 10% throughout a two year storage period.

A desiccating stopper is available from West Pharmaceutical Services (Pheonixville, Pennsylvania, USA), as a LyoDry™ stopper. This has a moisture capacity which approximately 5% of the mass of the stopper . with an initial uptake rate of 0.04mg/cm^2/day which then decreases over a period of time.

Preferred vials for use in the present invention are of generally conventional construction, the mouth opening being defined by the rim of the neck of the vial. Preferably, the vial is made of a moisture-impermeable material, such as glass. Preferred vials will have a nominal capacity in the range 5 to 150 ml, more preferably about 20 ml for the 1.1g formulation and 100ml for the 2.2g formulation.

The present invention also provides a method of desiccating a formulation of the present invention, which comprises enclosing the said formulation in a vial and maintaining a stopper formed from an elastomeric material compounded with a desiccant material in contact with the atmosphere inside the vial. This method may be a method of long-term storage and/or protection against hydrolysis during storage.

An alternative desiccant stopper for use with a formulation of the present invention is described in WO 95/25045 (SmithKline Beecham). This is formed from an elastomer which has an annular groove on the inwardly facing region which accommodates a pre-formed ring of desiccant material such as molecular sieve, separated from the interior of the vessel by a semi-permeable membrane.

An alternative dessicating means for use with a formulation of the present invention, a so-called "leaky vial", is described in WO 95/34488 (SmithKline Beecham). This comprises a vial formed from a material which is permeable to water vapour but impermeable to liquid water and provided with a puncturable seal. The vial is enclosed within an outer container which is less permeable to water vapour, the intermediate space between the outer container and the inner vial containing a desiccant.

In a further variant, a conventional vial and stopper may be used, with desiccating means provided by a pharmaceutically acceptable water soluble inorganic desiccant such as desiccating metal salt, for instance sodium chloride, calcium chloride or magnesium chloride, which is co-formulated with the crystalline sodium amoxycillin and potassium clavulanate (see WO 95/33487, SmithKline Beecham).

A formulation of the invention may be manufactured using techniques which are generally conventional in the field of manufacture of injectable formulations. For instance, crystalline sodium amoxycillin and potassium clavulanate may be mixed in a nominal 10:1 ratio and the bulk formulation then filled into vials, under sterile conditions.

Formulations of the present invention may be used in treating bacterial infections, by bolus or infusion administration of a reconstituted solution thereof. Accordingly, in a further aspect, the present invention provides for a pharmaceutical formulation as hereinbefore defined, for use in therapy.

Preferably, the formulations are used for short term treatment of bacterial infections, for instance:
Upper Respiratory Tract Infections (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media, typically caused by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pyogenes*;
Lower Respiratory Tract Infections e.g. acute exacerbations of chronic bronchitis, lobar and bronchopneumonia, typically caused by *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*;
Genito-urinary Tract Infections e.g. cystitis, urethritis, pyelonephritis, female genital infections, typically caused by *Enterobacteriaceae* (mainly *Escherichia coli*), *staphylococcus saprophyticus* and *Enterococcus species*, and gonorrohoea caused by *Neisseria gonorrhoeae*;
Skin and Soft Tissue Infections typically caused *by Staphylococcus aureus, Streptococcus pyogenes* and *Bacteroides species*;
Bone and Joint Infections e.g. osteomyelitis, typically caused by *Staphylococcus aureus*, where more prolonged therapy may be appropriate; and
Other Infections e.g. septic abortion, puerperal sepsis, intra-abdominal sepsis, septicaemia, peritonitis, post surgical infections.

The 1000/200mg formulation may also be used prophylaxis against infection which may be associated with major surgical procedures such as gastro-intestinal, pelvic, head and neck, cardiac, renal, joint replacement and biliary tract surgery. The 2000/200mg formulation may also be used for prophylaxis against infection caused by susceptible organisms in gastro-intestinal surgery.

Preferably, for more severe infections, the dosage is 1.1g every eight hours or 2.2g every 12 hours.

The invention will now be described by way of non-limiting examples only.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Example 1 – desiccant stopper

A desiccant elastomeric material was made having the following composition:

Chemical name	Function	phr
Chlorinated butyl rubber	rubber base	100
Talc	filler	20
Calcined clay	filler	20
Molecular sieve 4A	desiccant	40
Zinc oxide	acid acceptor	4
Brominated phenolic resin	curing agent	5
Stearic acid		2
Polyethylene	lubricant	3

This composition was compounded via a conventional process, as broadly outlined above, and was made into stoppers for pharmaceutical vials of a shape and size identical to conventional stoppers made of conventional non-desiccating elastomers, and having a puncturable region as described above.

The composition of Example 1 may be modified, for example varying within ± 10% of that listed above.

Ten 20 mm stoppers made as described above were stored for 24 hours at room temperature in a 75% relative humidity environment. After 24 hours the stoppers gained an average weight of 2.0 mg each, indicating a significant amount of moisture uptake.

Example 2 – pharmaceutical formulation

Crystalline anhydrous sodium amoxycillin (EP 0 131 147-A1) and potassium clavulanate in the weight ratio 10:1 were blended together in bulk (scale approximately 100kg total), at a relative humidity of less than 30%

Glass vials were then filled with either 2000mg sodium amoxycillin and 200mg potassium clavulanate or 1000mg sodium amoxycillin and 100mg potassium clavulanate on a standard vial filling line and 20mm desiccant stoppers (WO 97/29151) inserted.

(All weights are expressed as free acid equivalent, due allowance also being made for potency.)

Example 3 – Intravenous Infusion

A vial (50ml) containing 1.1 gram or 2.2 gram is reconstituted by adding approximately 20 mL of 0.9% Sodium Chloride Injection, USP, and shaking well, and immediately diluting to a total volume of 100 mL. The solution of reconstituted drug is then be administered over a period of 60 minutes by direct infusion.

Stability: The 1.1g formulation is stable for 120 minutes after final dilution and should be administered no more than 60 minutes after reconstitution. The 2.2g formulation is stable for 90 minutes after final dilution and should be administered no more than 30 minutes after reconstitution.

Example 4 - Clinical Pharmacology of an intravenous (IV) formulation of Amoxycillin/Clavulanate (A/C).

The purpose of this study was to determine and compare A & C pharmacokinetics after IV and oral administration, integrating these data with defined pharmacodynamic (PD) correlates. In an open, randomized, 3-part, single dose, crossover study, 15 healthy volunteers received at each session an infusion of 1000/100mg (1.1g) or 2000/200 (2.2g) A/C over a period of 60 minutes or a single oral dose of 875/125mg A/C. The wash-out period was at least three days and each subject received each of the three doses once. Twelve timed blood samples were obtained after each dose and analyzed by HPLC. IV and oral A/C were well tolerated. A & C disposition was linear over the 3.5 fold dose range. Half-life, distribution volume, and clearance were independent of dose or route of administration, averaging 1.2 [0.1] hr, 29 [2.3] L, and 16 [0.3] L/hr for A and 1 [0.03] hr, 22 [1.2] L, and 15.3 [0.5] L/hr for C, respectively. PD modelling demonstrated the appropriateness of A/C IV 1.1g q12h for infections due to pathogens with an amoxycillin MIC <= 2 mg/L, while an IV A/C dose of 1.1g q8h or 2.2g q12h for infections is appropriate for pathogens with an amoxycillin MIC <= 4 mg/L. These data define the interchangeability of IV amoxycillin/clavulanate with the currently available 875/125 mg oral formulation.

Claims

1. A pharmaceutical formulation adapted for intravenous administration and consisting essentially of crystalline sodium amoxycillin and potassium clavulanate in the weight ratio 10:1.

2. A pharmaceutical formulation provided as a unit dosage which comprises 2000mg crystalline sodium amoxycillin and 200mg potassium clavulanate, within a tolerance of ±10%.

3. A formulation as claimed in claim 2 in which the formulation has no added excipients or carriers.

4. A pharmaceutical formulation provided as a unit dosage which comprises 1000mg crystalline sodium amoxycillin and 100mg potassium clavulanate, within a tolerance of ±10%.

5. A pharmaceutical formulation provided as a unit dosage which consists essentially of 1000mg crystalline sodium amoxycillin and 100mg potassium clavulanate, within a tolerance of ±10%.

6. A formulation as claimed in any one of claims 1 to 5 in which the crystalline sodium amoxycillin is anhydrous.

7. The use of crystalline sodium amoxycillin and potassium clavulanate in the manufacture of a medicament consisting of a unit dosage consisting of 2000mg amoxycillin and 200mg clavulanate, for administration in a twice a day or a three times a day dosage regimen.

8. The use of crystalline sodium amoxycillin and potassium clavulanate in the manufacture of a medicament consisting of a unit dosage consisting of 1000mg amoxycillin and 100mg clavulanate, for administration in a twice a day or a three times a day dosage regimen.

9. A vial provided with desiccating means and containing a formulation as claimed in any one of claims 1 to 6.

10. A vial as claimed in claim 9 in which the desiccating means is a desiccant stopper made at least in part from a desiccant elastomeric material.

11. A vial as claimed in claim 10 in which the desiccant elastomeric material comprises an elastomeric base material selected which is a halogenated butyl rubber.

12. A vial as claimed 10 or 11 in which the desiccant elastomeric material comprises a filler present in the range from 0 to 110phr.

13. A vial as claimed in any one of claims 10 to 12 in which the filler is a talc or a clay, a mixture thereof.

14. A vial as claimed in any one of claims 10 to 13 in which the desiccant elastomeric material comprises a desiccant material which is an inorganic desiccant material.

15. A vial as claimed in claim 14 in which the inorganic desiccant material is a molecular sieve or calcium oxide.

16. A vial as claimed in claim 14 or 15 in which the inorganic desiccant material is present in the range 20 to 100phr.

17. A vial as claimed in any one of claims 10 to 16 in which the desiccant elastomeric material from which desiccant stoppers may be formed comprises as its essential ingredients (within ±10% tolerance):

Halogenated butyl rubber	100phr;
Talc, clay or talc/clay mixture (filler)	40;
Molecular sieve desiccant	40;

plus curative, acid acceptor, processing aids and pigment, present in from 0.5 to 15phr (combined total).

18. A vial as claimed in any one of claims 10 to 17 in which the desiccant stopper is made wholly of desiccant elastomeric material.

19. A vial as claimed in any one of claims 10 to 18 in which the stopper comprises a puncturable region in direct communication with the interior of the vial.

20. A vial as claimed in any one of claims 9 to 19 which is made of glass.

21. A formulation as defined in any one of claims 1 to 6 for use in therapy.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/06192

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/43 B65D81/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K B65D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 04189 A (SMITHKLINE BEECHAM PLC ;TASKIS CHARLES BERNARD (GB); HOLLAND SIMON) 15 February 1996 (1996-02-15) cited in the application page 1, line 32 -page 2, line 12 page 3, line 31 -page 4, line 20 page 5, line 23 - line 25	1,4-6, 8-16, 18-21
Y	page 9, line 7 - line 17	17
Y	WO 97 29151 A (WEST COMPANY UK LIMITED ;FRAMPTON NICHOLAS (GB); JANSSEN ANDRE (DE) 14 August 1997 (1997-08-14) cited in the application claims	17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 1999	02/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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